Stoke Therapeutics Presents Zorevunersen Data Showing Substantial Reductions in Seizures and Improvements in Multiple Measures of Cognition and Behavior That Support the Potential for Disease Modification in Dravet Syndrome

September 10, 2024

– New data showed improvements in cognition and behavior during the first year of treatment with additional increases demonstrated as treatment continued –

– Clinical effects observed across the Phase 1/2a and open-label extension studies (OLEs) of zorevunersen are a first in the treatment of Dravet syndrome and support plans for the Company's Phase 3 registrational study –

– Zorevunersen generally well-tolerated across the studies –

– Data presented for the first time at the 15th European Epilepsy Congress (EEC) –

BEDFORD, Mass.--(BUSINESS WIRE)--Sep. 10, 2024-- Stoke Therapeutics, Inc. (Nasdaq: STOK), a biotechnology company dedicated to restoring protein expression by harnessing the body's potential with RNA medicine, today announced highlights from presentations at the 15th European Epilepsy Congress (EEC) related to the Company's work to develop the first disease-modifying medicine for Dravet syndrome. Zorevunersen (STK-001) data showing substantial and sustained reductions in seizures and meaningful improvements in multiple measures of cognition and behavior were presented for the first time in a scientific forum. New data from an analysis of patients treated in the Phase 1/2a ADMIRAL study showed improvements in cognition and behavior during the first year of treatment with additional increases demonstrated as treatment continued. In addition, data from a two-year natural history study presented at the meeting showed that despite treatment with standard-of-care antiseizure medications, patients with Dravet syndrome continued to have high seizure rates and plateaued in their neurodevelopment, resulting in a widening gap in development compared to their neurotypical peers.

Dravet syndrome is a severe and progressive genetic epilepsy characterized by frequent, prolonged and refractory seizures beginning within the first year of life. The disease is classified as a developmental and epileptic encephalopathy due to the developmental delays and cognitive impairment associated with the disease. There are no approved disease-modifying therapies for people living with Dravet syndrome, which occurs in one out of 16,000 babies.

"The profound reductions in seizures and improvements in cognition and behavior seen in these studies open the door to a new era in the treatment of Dravet syndrome and provide convincing evidence of the potential for zorevunersen as the first disease-modifying medicine," said Helen Cross, MB ChB, Ph.D., Professor, The Prince of Wales's Chair of Childhood Epilepsy and Director of University College London Great Ormond Street Institute of Child Health, Honorary Consultant in Paediatric Neurology, and the ADMIRAL study lead investigator. "We are very encouraged by the data from the Phase 1/2a ADMIRAL study that showed substantial reductions in seizures and meaningful improvements in cognition and behavior within the first year of treatment. As patients continue treatment in the open-label extension study we see even greater improvements in their cognition and behavior, which is remarkable."

"The two-year natural history data provide clear evidence that current anti-seizure medicines are insufficient because even with the best available medicines patients still suffer from continued high rates of seizures and, as these children age, their development falls further behind their neurotypical peers," said Barry Ticho, M.D., Ph.D., Chief Medical Officer of Stoke Therapeutics. "Data from our clinical studies of zorevunersen provide a glimpse into the future of treatment for patients with Dravet syndrome. The data from our studies suggest that by restoring protein expression with zorevunersen, we may be able to substantially reduce seizures beyond any benefit patients are currently receiving from anti-seizure medicines. Even more promising is the potential to improve cognition and behavior, which has never before been demonstrated in a clinical study of Dravet syndrome. These data provide confidence in our plans for a Phase 3 registrational study, including the dose regimen and clinical endpoints."

Highlights from the Company's presentations at the meeting include:

- MONARCH and ADMIRAL Phase 1/2a studies [Paediatric Epileptology Session: Tuesday, September 10 at 12:22PM CEST]: Single and multiple doses of zorevunersen up to 70mg were generally well tolerated. Patients treated with 2 or 3 doses of 70mg of zorevunersen experienced median seizure reductions of 85% (n=10) at 3 months and 74% (n=9) at 6 months after the last dose, compared to baseline. Multiple doses of zorevunersen (30mg, 45mg, or 70mg) led to meaningful improvements in multiple measures of cognition and behavior within the first year of treatment, including receptive communication, interpersonal relationships and gross motor skills.

- SWALLOWTAIL and LONGWING open label extension (OLE) studies [Poster: P875]: Safety findings among patients who continued treatment were consistent with the findings from the Phase 1/2a studies, except for a greater incidence of cerebrospinal fluid protein elevation. Durable reductions in convulsive seizure frequency were observed throughout the course of treatment. In addition, data indicated meaningful improvements in multiple measures of cognition and behavior over the first year of continued dosing of zorevunersen.

- BUTTERFLY (natural history study) [Poster: P788]: Compared to their neurotypical peers, adaptive functioning and neurodevelopment in patients with Dravet syndrome generally plateaued, resulting in a widening developmental gap over time. Seizure rates remained high over 24 months despite treatment with standard-of-care antiseizure medications.

All presentations are available for download on the Stoke Therapeutics website under the Investors & News tab.

About Dravet Syndrome

Dravet syndrome is a severe and progressive genetic epilepsy characterized by frequent, prolonged and refractory seizures, beginning within the first year of life. Dravet syndrome is difficult to treat and has a poor long-term prognosis. Complications of the disease often contribute to a poor quality of life for patients and their caregivers. The effects of the disease go beyond seizures and often include intellectual disability, developmental delays, movement and balance issues, language and speech disturbances, growth defects, sleep abnormalities, disruptions of the autonomic nervous system and mood disorders. The disease is classified as a developmental and epileptic encephalopathy due to the developmental delays and cognitive impairment associated with the disease. Compared with the general epilepsy population, people living with Dravet syndrome have a higher risk of sudden unexpected death in epilepsy, or SUDEP. There are no approved disease-modifying therapies for people living with Dravet syndrome. One out of 16,000 babies are born with Dravet syndrome, which is not concentrated in a particular geographic area or ethnic group.

About Zorevunersen (STK-001)

Zorevunersen is an investigational new medicine for the treatment of Dravet syndrome currently being evaluated in ongoing clinical trials. Stoke believes that zorevunersen, a proprietary antisense oligonucleotide (ASO), has the potential to be the first disease-modifying therapy to address the genetic cause of Dravet syndrome. Zorevunersen is designed to upregulate NaV1.1 protein expression by leveraging the non-mutant (wild-type) copy of the *SCN1A* gene to restore physiological NaV1.1 levels, thereby reducing both occurrence of seizures and significant non-seizure comorbidities. Zorevunersen has been granted orphan drug designation by the FDA and the EMA, and rare pediatric disease designation by the FDA as a potential new treatment for Dravet syndrome.

About the U.S. Studies: MONARCH (Phase 1/2a) and SWALLOWTAIL (OLE)

The MONARCH study was a Phase 1/2a open-label study of children and adolescents ages 2 to 18 who have an established diagnosis of Dravet syndrome and have evidence of a genetic mutation in the *SCN1A* gene. The primary objectives for the study were to assess the safety and tolerability of zorevunersen (STK-001), as well as to determine the pharmacokinetics in plasma and exposure in cerebrospinal fluid. A secondary objective was to assess the efficacy as an adjunctive antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency.

Following completion of MONARCH, patients who met study entry criteria were eligible to continue treatment in SWALLOWTAIL, an open-label extension (OLE) study designed to evaluate the long-term safety and tolerability of repeat doses of zorevunersen. The study is also evaluating the long-term effects of zorevunersen on convulsive seizure frequency and on behavior, cognition and overall quality of life. Dosing in SWALLOWTAIL is ongoing.

About the UK Studies: ADMIRAL (Phase 1/2a) and LONGWING (OLE)

The ADMIRAL study was a Phase 1/2a open-label study of children and adolescents ages 2 to <18 who have an established diagnosis of Dravet syndrome and have evidence of a genetic mutation in the *SCN1A* gene. The primary objectives for the study were to assess the safety and tolerability of multiple doses of zorevunersen (STK-001), as well as to determine the pharmacokinetics in plasma and exposure in cerebrospinal fluid. A secondary objective was to assess the effect of multiple doses of zorevunersen as an adjunctive antiepileptic treatment with respect to the percentage change from baseline in convulsive seizure frequency. Overall clinical status and quality of life were secondary endpoints of ADMIRAL.

Following completion of ADMIRAL, patients who met study entry criteria were eligible to continue treatment in LONGWING, an open-label extension (OLE) study designed to evaluate the long-term safety and tolerability of repeat doses of zorevunersen. The study is also evaluating the long-term effects of zorevunersen on convulsive seizure frequency and on behavior, cognition and overall quality of life. Dosing in LONGWING is ongoing.

About the BUTTERFLY Observational Study

The BUTTERFLY study was a multicenter, longitudinal, prospective, observational study of children and adolescents ages 2 to 18 who have been diagnosed with Dravet syndrome as a result of an *SCN1A* gene mutation. This study was designed to evaluate neurodevelopmental status and change from baseline to 24 months. Secondary and exploratory endpoints in the study evaluated changes in other disease measures, including seizures and additional non-seizure comorbidities. No investigational medications or other treatments were provided. Participants continued to receive their usual care, including anti-seizure medications, and were observed for up to two years. The study was conducted at approximately 20 sites in the United States. Two-year results were presented at the American Epilepsy Society Annual Meeting in December 2023 and showed that, on average, patients experienced no meaningful improvement in convulsive seizure frequency and exhibited widening gaps in cognition and behavior compared to neurotypical peers, despite treatment with the best available anti-seizure medicines.

About Stoke Therapeutics

Stoke Therapeutics (Nasdaq: STOK), is a biotechnology company dedicated to restoring protein expression by harnessing the body's potential with RNA medicine. Using Stoke's proprietary TANGO (Targeted Augmentation of Nuclear Gene Output) approach, Stoke is developing antisense oligonucleotides (ASOs) to selectively restore protein levels. Stoke's first compound, zorevunersen (STK-001), is in clinical testing for the treatment of Dravet syndrome, a severe and progressive genetic epilepsy. Dravet syndrome is one of many diseases caused by a haploinsufficiency, in which a loss of ~50% of normal protein levels leads to disease. Stoke is pursuing the development of STK-002 for the treatment of autosomal dominant optic atrophy (ADOA), the most common inherited optic nerve disorder. Stoke's initial focus is haploinsufficiencies and diseases of the central nervous system and the eye, although proof of concept has been demonstrated in other organs, tissues, and systems, supporting its belief in the broad potential for its proprietary approach. Stoke is headquartered in Bedford, Massachusetts with offices in Cambridge, Massachusetts. For more information, visit https://www.stoketherapeutics.com/.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995, including, but not limited to: the ability of zorevunersen to treat the underlying causes of Dravet syndrome and reduce seizures or show improvements in non-seizure comorbidities and the timing and expected progress of clinical trials, regulatory meetings and regulatory decisions. Statements including words such as “expect,” “plan,” “will,” “continue,” or “ongoing” and statements in the future tense are forward-looking statements. These forward-looking statements involve risks and uncertainties, as well as assumptions, which, if they prove incorrect or do not fully materialize, could cause our results to differ materially from those expressed or implied by such forward-looking statements, including, but not limited to, risks and uncertainties related to: the Company’s ability to advance, obtain regulatory approval of, and ultimately commercialize its product candidates, including zorevunersen; the timing of data readouts and interim and final results of preclinical and clinical trials; the receipt and timing of potential regulatory decisions; positive results in a clinical trial may not be replicated in subsequent trials or successes in early stage clinical trials may not be predictive of results in later stage trials; the Company’s ability to fund development activities and achieve development goals; the Company’s ability to protect its intellectual property; the direct or indirect impact of global business, political and macroeconomic conditions, including inflation, interest rate volatility, cybersecurity events, uncertainty with respect to the federal budget, instability in the global banking system and volatile market conditions, and global events, including public health crises, and ongoing geopolitical conflicts, such as the conflicts in Ukraine and the Middle East; and other risks and uncertainties described under the heading “Risk Factors” in the Company’s Annual Report on Form 10-K for the year ended December 31, 2023, its quarterly reports on Form 10-Q, and the other documents it files from time to time with the Securities and Exchange Commission. These forward-looking statements speak only as of the date of this press release, and the Company undertakes no obligation to revise or update any forward-looking statements to reflect events or circumstances after the date hereof.

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